

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of:

Rossen, Kai, *et al.*

Appl. No.: 10/591,340

Filed: August 31, 2006

For: **Process for Preparing N-protected
4-Ketoproline Derivates**

Art Unit: 1626

Examiner: Sun Jae Loewe

Atty. Dkt.: 7601/88254

Conf. No: 9531

Declaration Under 37 C.F.R. § 1.132

Commissioner of Patents
U.S. Patent and Trademark Office
Randolph Building
401 Dulany Street
Alexandria, VA 22314

Sir:

The undersigned, Dr. Günter Knaup, declares as follows:

1. I am, at present, Director of Process Research at Evonik Degussa GmbH, which is the owner of all right title and interest in the above-captioned application. In this function, I am responsible for the process development for pharmaceutical ingredients or intermediates and, *inter alia*, for 4-ketoproline derivatives.
2. I have a Ph.D. (German doctors degree Dr. Ing.) in the field of chemistry from the Institute of Organic Chemistry, Technical University of Darmstadt, Germany. I have conducted research in the area of organic chemistry for more than 25 years.
3. I have reviewed the Office Action for the above application dated April 21, 2008, the final rejection dated February 18, 2010 and the references that were used in rejecting the claims, *i.e.*, Dormoy, *et al.* (*Synthesis*, pg. 81-86 (1986)), Carlsen, *et al.*, (*J. Org. Chem.* 46:3936-3938 (1981)), Riley, *et al.*, (*J. Chem. Soc., Chem. Commun.*, 1530-1532 (1983)) and Narukawa, *et al.* (*Tetrahedron* 53:539-556 (1997)).

4. It is my opinion that the references that were cited in the Office Action do not contain teachings, when considered either alone or in combination, that would provide one of skill in the art of organic chemistry with a reasonable expectation that the process claimed in the present application would succeed. I base this opinion on the following facts and evidence:

- a. Dormoy teaches that N-protected ketoproline esters can be prepared by oxidation of the corresponding N-protected hydroxyproline esters using sodium metaperiodate and ruthenium dioxide. The reaction is carried out in a biphasic system consisting of tetrachloromethane and water. Dormoy does not suggest that this reaction could be run in an aqueous one phase system alone.

As pointed out in the description of the present application, 4-ketoproline derivatives are unstable compounds under the reaction conditions applied. The processes for producing these unstable compounds, however, are based on the use of very strong oxidizing agents. Dormoy therefore uses a biphasic system to withdraw the oxidation product from the aqueous phase containing the oxidizing agent into an organic phase. The present invention aims to simplify this process, reduce the need for organic solvents and yield a very pure reaction product without the need for an extraction. Prior art processes like those disclosed in Dormoy which require an extraction, therefore cannot provide a reasonable expectation that the process claimed by Applicants would succeed.

- b. Carlsen teaches that oxidations using ruthenium dioxide and periodate usually failed when carboxylic acids are present or generated during the reaction (page 3936). According to this publication this issue can be solved by adding acetonitrile as a co-solvent. Nevertheless, Carlsen used a standard biphasic system consisting of tetrachloromethane and water and, even with the use of acetonitrile as co-solvent, the solvent system remains biphasic

Carlsen, taken alone or in combination with Dormoy, would not suggest to a skilled artisan to carry out oxidations in the manner claimed by Applicants. In addition, Carlsen seems contradictory to Narukawa which presents results suggesting that acids may not have a negative effect on oxidations performed using the ruthenium oxide/periodate system.

- c. Riley teaches the catalytic oxidation of tert.-amines with molecular oxygen in a homogenous aqueous solution to produce the corresponding N-oxide. N-protected hydroxyprolines, *i.e.*, the substrate of the process according to the present invention, are not tertiary amines. From a chemist's point of view the substrates (tert.-amines) disclosed in Riley are completely different from N-protected hydroxyprolines.

In addition, the products obtained by Riley (N-oxides) are not ketoproline compounds and ketoproline compounds are not encompassed by the term "N-oxides."

The reasons for the superior results of Riley using water as solvent were associated with stabilizing effects of water on the N-oxide products (see Riley, pg. 1531 left column). A similar effect on ketoprolines does not exist and was never proposed.

Since the reaction described by Riley has essentially nothing in common with the process according to the present invention, this reference is not relevant to the present invention either taken alone or in combination with the other references cited by the Examiner.

- d. Narukawa teaches the oxidation of tert.-butoxycarbonyl-4-hydroxyproline with sodium metaperiodate and ruthenium oxide using a biphasic solvent system consisting of water and ethyl acetate. It cannot be concluded from this publication that the product tert.-butoxycarbonyl-4-oxoproline is not largely soluble in water. The extraction of product from the aqueous layer in a twofold extraction with ethyl acetate is described (p 549). However, this just indicates that the product is reasonably soluble in water, thus requiring a second extraction step to be removed completely. Therefore, Narukawa does not suggest that Applicant's process might work.

Further, it should be borne in mind that ketoproline compounds are amino acid derivatives. Amino acids generally show good solubility in water or aqueous solutions. Thus, a person skilled in the art would expect good water solubility for ketoproline compounds rather than low water solubility.

- e. In summary, Dormoy and Carlson only disclose extractions in a biphasic system. In contrast, the process of the present invention does not require a complicated extraction process for removal of the reaction product from the oxidation system. Possible further oxidation of the reaction product and formation of byproducts is avoided in a simple and, in view of Dormoy and Carlsen, unexpected manner.

Although Riley carries out an oxidation in an aqueous one phase system, neither the starting substances nor the end products are comparable to hydroxyproline or ketoproline. Therefore, Riley cannot provide a reasonable expectation that the process claimed in the present application will succeed. In addition, Riley does not carry out a crystallization and therefore does not address the problem of how the formation of byproducts could be avoided.

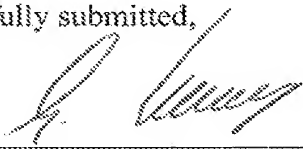
Like Dormoy and Carlson, Narukawa only teaches the use of biphasic systems. Regarding the solubility of ketoproline, the only teaching, if any, that may be present is that ketoprolines have reasonably good solubility in water and therefore do not precipitate easily.

Based upon the above considerations, it is my opinion that one of skill in the art could not have reasonably predicted the success of the reaction of the present claims based upon the combination of Dormoy, Carlsen, Riley and Narukawa.

5. I further declare that all statements made herein on the basis of personal knowledge are true, and all statements made on information and belief are believed to be true; and further that any willful false statements or the like so made are punishable by fine or imprisonment or both under Section 1011 of Title XVIII of the United States Code; and that such willful false statements may jeopardize the validity of the above-captioned application or any patent issuing thereon.

Respectfully submitted,

November 25, 2010
Date



Günter Knaup